Remarks

The final office action mailed October 2, 2002 has been received and reviewed. All pending claims stood rejected. An interview concerning the application and office action was held on February 20, 2003. Applicants would like to thank the Examiner and her supervisor for the courtesy extended their representative at the interview. As discussed at the interview, applicants are submitting a request for continued examination along with this amendment and respectfully request reconsideration of the rejected claims.

1. Claim Objections

Claims 9, 12-15, and 17-18 were objected to as being of improper dependent form. Claim 12 was previously cancelled, making the objection as to this claim moot. Claim 18 has been cancelled without prejudice or disclaimer, making the objection as to this claim moot. Claims 13-15 and 17 have been amended to remove the term "shelf life." Claim 14 has also been amended to recite that the time period is "at least 1 year" to address the objection that claim 17 does not further limit claim 14. In view of these amendments, applicants respectfully request that the objections be withdrawn.

2. Claim Rejections-35 U.S.C. § 102

Claims 1-3, 7, and 9 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Sas *et al.* (EP 389035 A1) ("Sas"). Applicants respectfully traverse the rejection.

As discussed at the interview, the presently claimed invention is not anticipated by Sas. As amended, independent claim 1 recites a composition comprising (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, the composition further comprising less than 0.5% by weight (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one. Claims 2 and 3 depend from claim 1.

In contrast, Sas discloses a pharmaceutical composition having a crystalline pure form of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one. (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one is known to be a polymorphous compound and

has two crystalline pure forms, referred to as "Form 1" and "Form 2." Sas discloses methods of preparing both Form 1 and Form 2 using different crystallization conditions. Form 1 is crystallized from a polar solvent while Form 2 is crystallized from an apolar solvent. These methods provide crystalline pure Form 1 or Form 2, which means that the composition of one crystalline form of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, *i.e.*, Form 1, is substantially free of the other crystalline form, *i.e.*, Form 2.

Sas does not disclose that (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is present in an amount less than 0.5% by weight in a composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one because Sas does not discuss a chemical purity of its composition. Rather, the purities disclosed in Examples 1-8 of Sas are the crystalline purities of Form 1 and Form 2 of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, as determined by DRIFT analyses. Therefore, the 97.2% purity disclosed in Example 2 refers to a compound that is 97.2% Form 1 of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one. In addition, Sas does not disclose that compounds different from (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one (*i.e.*, impurities) are present in its composition, let alone that any such impurities include (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one. Furthermore, as known in the art, DRIFT analyses are not suitable for detecting impurities at a level below 1% and, therefore, Sas could not disclose the presence of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount less than 0.5% by weight.

Applicants submit herewith a Declaration under C.F.R. § 1.132 describing NMR spectra for two samples of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one. Both samples have a physical, crystalline purity of greater than 98% of Form 1, as determined by ^{13}C NMR. As determined by ^{1}H NMR, Sample A has 2.4% (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one and Sample B has 0.3% (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one. Since Sample B has less of the impurity than Sample A, the chemical purity of Sample B is significantly higher than that of Sample A.

The ^{13}C NMR spectra also support that Sample B has substantially less (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one than Sample A. In Sample A, the (7α,

17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one was present at approximately 2.1% while in Sample B, no (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one was detected. Therefore, the ^{1}H and ^{13}C NMR spectra show that the composition of the present invention comprises less than 0.5% by weight (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one relative to the (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one.

In contrast, the solid state ^{13}C NMR spectrum of Form 1 in Sas *et al.* does not indicate the chemical purity of the product with respect to the impurity (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one. Moreover, the chemical purity cannot be determined given the signal to noise ratio in the relevant portion (between 200-205 ppm) of the spectrum.

Furthermore, since both samples have a crystalline purity of greater than 98% of Form I and differing amounts of the (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one, the NMR spectra also indicate that the crystalline purity and the chemical purity of the two products are distinct.

Since Sas does not disclose that (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is present in its composition as an impurity or that this impurity is present in an amount less than 0.5% by weight, Sas cannot anticipate claim 1.

The argument that Sas anticipates claim 1 because Sas is silent about impurities (and, therefore, discloses 0% by weight of the impurity) fails because Sas does not disclose (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one as an impurity. As previously discussed, Sas does not disclose this impurity in its composition because Sas discloses a crystalline pure form of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one and does not discuss the chemical purity of the compounds. Furthermore, the DRIFT analyses used in Sas are not suitable for detecting impurities below 1% and would not detect the amount of impurity recited in claim 1.

If the argument is that Sas inherently discloses the claimed composition, then that argument too fails. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. Inherency, however, may not be

established by probabilities or possibilities.'" (M.P.E.P. § 2112, *quoting In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949 (Fed. Cir. 1999)). As further stated by the Federal Circuit "[t]o serve as anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such [extrinsic] evidence must make clear that the missing descriptive is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991).

Since Sas does not disclose every element of claim 1, applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn. Applicants also request that the rejection of claims 2-3, which depend directly from claim 1, be withdrawn.

Independent claim 7 recites a pharmaceutical dosage unit comprising a pharmaceutically suitable solid carrier and a composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, which comprises (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount less than 0.5% by weight.

Since Sas does not disclose that (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is present in its composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, applicants respectfully request that the rejection of claim 7 be withdrawn for the same reasons presented above.

As amended, independent claim 9 recites a dosage unit of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, the dosage unit having a reduced content of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one over a time period. The dosage unit comprises a pharmaceutically suitable solid carrier, (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one in an amount of less than 2.50 mg per dosage unit, and less than 5% by weight of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one. Since Sas does not disclose that (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is present in its composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, applicants respectfully request that the rejection of claim 9 be withdrawn for the same reasons presented previously. Claim 9 is further allowable because Sas does not disclose that the dosage unit comprises less than 5% by weight of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-

pregn-4-en-20-yn-3-one.

3. Claim Rejections-35 U.S.C. § 103

A. Claims 4-6 - Sas and van Vliet

Claims 4-6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sas and van Vliet et al. (*Recueil des Travaux Chimiques des Pays-Bas*, April 1986, 105/4:111-115) ("van Vliet"). Applicants respectfully traverse this rejection, as hereinafter set forth.

Applicants respectfully submit that claims 4-6 are not rendered obvious by Sas. As discussed previously herein, Sas discloses a crystalline pure pharmaceutical composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, where the two forms of the polymorphous compound are crystallized using different conditions.

As amended, claim 4 recites an improvement in a process for preparing (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one having reduced impurities. The improvement comprises aging crystals of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one in the presence of water for a period of time of at least 24 hours. Claims 5 and 6 depend directly on claim 4. Applicants note that claim 4 does not recite any amount at which the impurities are present in the (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one.

Sas does not teach or suggest that its composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one is prepared by aging the crystals. Rather, Sas discloses that its composition of crystalline pure Form I is prepared by crystallizing (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one from a polar solvent. As described in Examples 1-4, the crystalline pure Form I is recrystallized from acetone and pyridine, ethanol and pyridine, or ethyl acetate and pyridine. The crystals are filtered, washed, and dried under vacuum. Crystalline pure Form II is prepared by crystallizing (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one from an apolar solvent. Example 5 discloses that the crystalline pure Form II is recrystallized from ethyl acetate, pyridine, and hexane. Nothing in Sas teaches or suggests that the crystals are aged in the presence of water.

van Vliet fails to correct these deficiencies in Sas. As acknowledged by the Examiner, van Vliet does not disclose aging the crystals for at least 24 hours. Office Action of July 31,

2001, p. 4. Rather, van Vliet discloses an alternative method of synthesizing (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one. The Examiner states that it would have been obvious to a person of ordinary skill in the art to increase the time period for aging the crystals because it was well within the skill of the artisan. *Id.* (*See also*, Office Action mailed October 2, 2002, p. 6.) However, it is known to a person of ordinary skill in the art that the quality of crystals typically does not improve if the crystals are allowed to age in the presence of residual solvents for a long period of time. Furthermore, claim 4 recites that the crystals are aged in the presence of water for a period of at least 24 hours. In conventional recrystallization processes, crystals are formed, filtered, washed, and then dried. (*See*, Roberts et al., "Modern Experimental Organic Chemistry," p. 66 and 70-72). Therefore, the crystals formed in a conventional recrystallization process are not aged in the presence of water, as recited in claim 4.

The Office Action states that van Vliet is relied upon for its teaching that (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is present in the composition. However, claim 4 does not recite that (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is present in the composition or that it is present in a particular amount. Therefore, this argument for the obviousness of claim 4 is not proper.

Neither Sas nor van Vliet teaches or suggests aging the crystals of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one to improve the purity and the stability of the compound. In addition, no motivation is present in either of these references to age the crystals. As previously mentioned, it is known to a person of ordinary skill in the art that the quality of crystals typically does not improve if the crystals are allowed to age in the presence of residual solvents for a long period of time. Therefore, aging the crystals to produce a more pure and more stable (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one is a surprising and unexpected result and, accordingly, is not obvious.

As the proposed combination of Sas and van Vliet fails to teach or suggest every element of the presently claimed invention, applicants respectfully submit that the presently claimed invention is not obvious over the combination of references. Reconsideration is respectfully requested.

B. Claims 10-11 and 13-18 - Sas and van Vliet

Claims 10-11 and 13-18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sas and van Vliet. Claim 18 has been cancelled without prejudice or disclaimer, making the rejection of claim 18 moot. Applicants respectfully traverse this rejection as to the remaining claims, as hereinafter set forth.

Claims 10, 11, and 13-17 depend from claim 9 and, therefore, include the limitations that the dosage unit comprises less than 2.50 mg per dosage unit of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one and less than 5% by weight of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one. Neither Sas nor van Vliet teaches or suggests the dosage unit or that the impurity is present in the dosage unit at less than 5% by weight. Therefore, applicants respectfully submit that the presently claimed invention is not obvious over this combination of references. Reconsideration is respectfully requested.

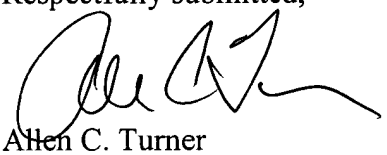
4. New claims 19 and 20

New claims 19 and 20 have been added to the pending claims. Applicants respectfully submit that these new claims define patentable subject matter.

Conclusion

In view of the remarks, applicants respectfully submit that claims 1-7, 9-11, 13-17, 19, and 20 define patentable subject matter. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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Enclosures

N:\1963\5047\amendment in support of RCE revised.wpd

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Three times amended) A composition [of] comprising (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, said composition further comprising less than 0.5% by weight (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one [in an amount less than 0.5% by weight].

2. (Three times amended) The composition [according to] of claim 1, wherein the amount of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is 0.25% or less by weight.

3. (Three times amended) The composition [according to] of claim 1, wherein the amount of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is 0.1% or less by weight.

4. (Three times amended) [A]An improvement in a process for preparing (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, the improvement comprising aging crystals of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one in the presence of water for a period of time of at least 24 hours.

5. (Amended) The [process according to]improvement of claim 4 wherein the [aging] period of time lasts 3-6 days.

6. (Amended) The [process according to] improvement of claim 4, wherein the crystals are formed in the last step of a synthesis comprising the steps of:

a. reacting (7α, 17α) -3, 3-dimethoxy-17-hydroxy-7- methyl-19-norpregn-5 (10) -en-20-yn-3-one in an organic solvent with a weak acidic aqueous solution,

b. pouring out the solution in water which is slightly alkaline, and

c. washing the crystals with water which is slightly alkaline.

9. (Three times amended) A dosage unit of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, said dosage unit having less than 5% by weight of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one over a time period, said dosage unit comprising:

a pharmaceutically suitable solid carrier, [and]

said (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one in an amount of less than 2.50 mg per dosage unit, and

[comprising] less than 5% by weight of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one [at a shelf-life of at least 1.5 years].

10. (Amended) The dosage unit [according to] of claim 9, wherein the (7α, 17α) -17-hydroxy-7-methyl-19-nor-17-pregn-5 (10) -en- 20-yn-3-one is present in an amount of 1.25 mg or less.

11. (Amended) The dosage unit [according to] of claim 9, wherein the (7α, 17α) -17-hydroxy-7-methyl-19-nor-17-pregn-5 (10) -en-20-yn-3-one is present in an amount of 0.625 mg or less.

13. (Amended) The dosage unit [according to] of claim 9, wherein at a [shelf life] time period of 6 months the amount of (7α, 17α) -17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is 3% or less by weight of the amount of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10) -en-20-yn-3-one.

14. (Amended) The dosage unit [according to] of claim [13] 9, wherein the [shelf life] time period is at least 1 year.

15. (Amended) The dosage unit according to claim [12] 9, wherein the [shelf life] time period is at least 2 years.

16. (Amended) The dosage unit of claim 13, wherein the amount of (7α, 17α) -17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is 2% or less by weight of the amount of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10) -en-20-yn-3-one.

17. (Amended) The dosage unit of claim 14, wherein the [shelf life] time period is at least 1½ years.